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Impact of menstrual cycle phase on endocrine effects of partial sleep restriction in healthy women

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Summary There is extensive evidence that sleep restriction alters endocrine function in healthy young men, increasing afternoon cortisol levels and modifying levels of other hormones that regulate metabolism. Recent studies have confirmed these effects in young women, but have not investigated whether menstrual cycle phase influences these responses. The effects on cortisol levels of limiting sleep to 3 h for one night were assessed in two groups of women at different points in their menstrual cycles: mid-follicular and mid-luteal. Eighteen healthy, young women, not taking oral contraceptives (age: 21.8 ± 0.53; BMI: 22.5 ± 0.58 [mean ± SEM]), were studied. Baseline sleep durations, eating habits and menstrual cycles were monitored. Salivary samples were collected at six times of day (08:00, 08:30, 11:00, 14:00, 17:00, 20:00) during two consecutive days: first after a 10 h overnight sleep opportunity (Baseline) and then after a night with a 3 h sleep opportunity (Post-sleep restriction). All were awakened at the same time of day. Women in the follicular phase showed a significant decrease ($p = 0.004$) in their cortisol awakening responses (CAR) after sleep restriction and a sustained elevation in afternoon/evening cortisol levels ($p = 0.008$), as has been reported for men. Women in the luteal phase showed neither a depressed CAR, nor an increase in afternoon/evening cortisol levels. Secondary analyses examined the impact of sleep restriction on self-reported hunger and mood. Menstrual cycle phase dramatically altered the cortisol responses of healthy, young women to a single night of sleep restriction, implicating effects of spontaneous changes in endocrine status on adrenal responses to sleep loss.

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1. Introduction

A number of population-based studies, both cross-sectional and longitudinal, have found that short sleep duration is associated with an increased risk for metabolic disorders such as obesity, the metabolic syndrome and Type 2 diabetes mellitus (Hasler et al., 2004; Choi et al., 2012; Kita et al., 2012). Laboratory-based studies involving either partial or total sleep deprivation for periods ranging from one to several nights have demonstrated acute changes in appetite and endocrine function. These have been interpreted as possible mediators of the impact of chronic short sleep on the increased risk for development of metabolic disorders (Leproult et al., 1997; Spiegel et al., 1999, 2004a; Wu et al., 2008; Markwald et al., 2013). Specifically, sleep loss has been reported to alter the levels of hormones, including cortisol (which affects glucose metabolism), leptin and ghrelin (which contribute to appetite regulation) (Morselli et al., 2012). In addition, sleep restriction has been shown to increase self-reported hunger and preferences for calorie-dense foods, and to disrupt carbohydrate metabolism (Spiegel et al., 1999, 2004a; Buxton et al., 2010). These changes have been reported to occur in the absence of increased tension or anxiety, which were considered to be likely markers of a nonspecific stress response to sleep loss (Spiegel et al., 2004b).

The adrenal hormone cortisol, which regulates many aspects of human physiology, can be measured from most bodily fluids, including saliva, which contains unbound cortisol (Kalman and Grahn, 2004). Under normal sleep/wake conditions, cortisol levels rise from low values during sleep to high values at the time of awakening in the morning, followed by a secondary rise ~30—45 min after awakening, known as the cortisol awakening response (CAR) (Pruessner et al., 1997). Following this morning peak, there is a steady decrease throughout the day to reach daily trough levels by approximately 12 h after awakening (Edwards et al., 2001; Wust et al., 2000; Taheri et al., 2004). Sleep loss alters this daily rhythm by causing a sustained elevation in afternoon cortisol levels, which has been linked to serious metabolic consequences, such as impaired lipid and glucose metabolism and increased risk of insulin resistance and metabolic syndrome (Plat et al., 1999; Whitworth et al., 2005; Anagnostis et al., 2009; Buxton et al., 2010).

Most laboratory studies of the endocrine effects of sleep loss have included only young male participants, probably because of the assumption that menstrual cycles in young women would complicate analyses of results. Studies of menstrual phase effects on spontaneous daily cortisol rhythms have yielded inconsistent findings, depending on their methodology. Results have included delays (Parry et al., 1994) or advances (Parry et al., 2000) of the daily cortisol rhythm during the late luteal phase, relative to the follicular phase, no change in morning cortisol values between the follicular and late luteal phases (Steiner et al., 1999; Kudielka and Kirschbaum, 2003), and no change in the timing and amplitude of cortisol rhythms between the follicular and luteal phases of the cycle (Bloch et al., 1998).

A few studies have examined the impact of sleep loss on cortisol rhythms in women (Patel et al., 2006; Omisade et al., 2010). A post hoc analysis of the self-reported menstrual cycles of participants in one of these studies suggested that menstrual phase could have modulated the impact of sleep loss. Dividing participants into those studied soon after the end of menstruation (presumed follicular phase) and those studied later (presumed luteal phase) indicated that the latter participants showed less change in cortisol rhythms after sleep loss. Women taking oral contraceptives showed an intermediate response. Because the subgroup sizes were small (3—4) and cycle timing involved only self reports, this post hoc analysis was not included in the original publication (Omisade et al., 2010).

The present study was designed to address this question directly by measuring the Baseline patterns of salivary cortisol levels during waking after a night with a 10 h sleep opportunity in young women during either their mid-follicular or mid-luteal phase, and comparing cortisol patterns to those after a single night with sleep restricted to a 3 h opportunity. Studies reporting that sleep restriction increased hunger ratings involved men exclusively, whereas those that showed no effect have included women (Spiegel et al., 2004a; Schmid et al., 2008; Brondel et al., 2010). Of the studies involving women only, no changes in hunger were reported after 4 nights of progressive sleep loss (Bosy-Westphal et al., 2008) or one night with a 3 h sleep opportunity (Omisade et al., 2010). The possibility that menstrual cycle phase could modulate effects of sleep loss on appetite and on mood changes has not been studied. Therefore, secondary outcome measures in this study included participants' self-reports of mood and hunger ratings.

2. Methods

2.1. Participants

Participants met the following inclusion criteria: self-identified female, 19—25 years of age, BMI of 18—30 (actual range recruited was 18—24.5, except for one in the luteal group with a BMI of 29.1), non-smoker, habitual daytime activity (i.e., no shift work), regular menstrual cycle, no travel over three or more time zones within 6 weeks prior to the study and habitual continuous sleep of 6—9 h nightly without frequent naps. Participants completed a Morningness—Eveningness Questionnaire; anyone with MEQ scores greater than 69 (extreme Morningness) or less than 31 (extreme Eveningness) were excluded (Horne and Ostberg, 1976). Exclusion criteria included a history of eating disorders; affective disorders (including post-traumatic stress disorder); chronic stress, anxiety or depression symptoms in the clinical range; sleep disorders; or ongoing hormone treatments, including hormonal birth control of any kind less than 3 months prior to taking part in the study. Professional or semi-professional athletes were excluded due to the potential for altered menstrual cycles resulting from intense training regimes.

The study was reviewed and approved by the Capital District Health Authority Research Ethics Board (Halifax, Nova Scotia, Canada) in accordance with the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. Potential participants were recruited by word-of-mouth and using notices and online advertising. All participants demonstrated understanding of the study

Table 1 Demographic characteristics of participants.

Measure	Follicular ($n = 9$)	Luteal ($n = 9$)
Age (years)	22.0 (2.7)	21.6 (1.9)
BMI	22.1 (1.9)	22.8 (3.0)
Progesterone (pg/mL)	***77.7 (8.1)**	**245.1 (9.3)**
Typical sleep (h)	8.06 (0.60)	8.14 (0.63)
Baseline night sleep (h)	8.3 (0.65)	8.15 (0.93)
Restricted night sleep (h)	2.86 (0.11)	2.85 (0.15)
Average menstrual cycle length (days)	30.1 (2.5)	29.8 (2.9)
Menstrual cycle range (days)	27—34.5	26—34

'Typical sleep' refers to the results obtained from actigraphy during the week before the laboratory portion of the study. Values that differed significantly between the two menstrual phase groups are shown in bold and marked by an asterisk. Values shown are mean (SD).

protocol and provided written informed consent before participating in the study.

Twenty women were recruited for the study; one withdrew after the first day due to illness, and another was excluded because she was not able to sleep at least 6 h during the first night in the laboratory. The remaining 18 women were pseudo-randomly assigned to one of the two menstrual phase groups to generate groups of equal size. Demographic characteristics for all included participants ($n = 18$) are reported in Table 1. We restricted recruitment to the period of January to April in order to avoid potential seasonal confounds. Of the 18 women studied, 5 participated in January/February and 13 participated in March/April. The results were consistent across these periods, and removing the data from the 5 January/February participants did not alter our results with respect to cortisol rhythms, mood scores or hunger ratings.

2.2. Materials/procedures

The approximate midpoint of the participants' follicular phase ($n = 9$) or luteal phase ($n = 9$) was determined on the basis of a minimum of two previous self-recorded menstrual cycles, so that each participant could be studied in the laboratory at the appropriate time. Several participants had available records of prior menstrual cycles, which tended to confirm the reliability of the two cycles they were required to record for the study. The range of average cycle lengths was 26—34.5 days for all participants (Table 1). For women with a 'standard' 28-day cycle, follicular and luteal phase midpoints are considered to fall on Days 8—10 and 20—22, respectively, with the onset of menses labeled Day 1 (Stricker et al., 2006). However, healthy young women may show menstrual cycle lengths ranging at least from 22—36 days (Fehring et al., 2006); therefore, women with cycles within this range were included, which made determining the midpoints of these phases more complicated.

There is considerable evidence that the variability in cycle length within and between women is largely attributable to variation in the follicular phase (menses to ovulation), with considerably less variability attributable to the luteal phase (Lenton et al., 1984; Wilcox et al., 2000; Fehring et al., 2006). The follicular phase can range from 12 to 24 days, while the luteal phase remains relatively stable at 12—14 days (Harlow and Ephross, 1995; Cole et al., 2009). Therefore, women with shorter cycles will have shorter follicular phases and earlier luteal phases relative to Day 1, and their phase midpoints will be correspondingly earlier, compared to women with longer cycles. The timing of the laboratory portion of the study, aimed at the approximate midpoint of each phase, was therefore adjusted to take this variation in cycle length into account. Since the laboratory study spanned nearly three days and scheduling conflicts made it difficult to start each participant precisely at the estimated midpoint of each phase, the actual timing of studies varied ±1—3 days from the estimated midpoint for some participants. Thus, participants were studied near the middle of their follicular and luteal phases, calculated based on the average lengths of 2—5 prior menstrual cycles and the timing of the last onset of menses. The average menstrual cycle lengths, number of menstrual cycles tracked, estimated timing of ovulation and actual days of the cycle studied, as well as progesterone levels, are shown for each participant in Supplementary Table S1; the mean and range of average cycle lengths for the two groups are shown in Table 1.

One week prior to the laboratory component of the study, each participant was given a food diary in which to record her daily food consumption, a sleep diary and a wrist actigraph (Motionlogger; Ambulatory Monitoring Inc., Ardsley, NY) to document her sleep pattern and to ensure that her habitual nightly sleep duration fell within the range of 6—9 h.

All participants spent 3 nights and 2 full days in the Chronobiology Laboratory at the Queen Elizabeth II Health Sciences Centre during the months of January—April, 2013. On the first night (Night 1, intended to habituate participants to the laboratory environment), participants came to the laboratory at approximately 22:00; they were weighed on a standard medical scale, and their height and weight were obtained in order to accurately determine their body-mass indices (BMIs) prior to taking part in the study. A single salivary sample was also taken at approximately 22:00 for measurement of progesterone levels, in order to confirm their expected menstrual cycle phase. Participants then went to a darkened bedroom in the laboratory and were allowed to sleep from 22:00 to 08:00 in order to habituate them to the laboratory environment. The next day, they were allowed to return to their usual schedule but cautioned against napping or drinking alcohol. Naps were not allowed during participation in the study. Actigraphs were worn during all nights in the laboratory in order to estimate sleep durations during the Baseline and Sleep-restriction nights.

On the second night (Night 2) in the laboratory, participants were allowed to sleep on the same schedule (i.e., up to 10 h) in darkness, but remained in the laboratory and adjacent hospital environment during the following day (Day 1; Baseline). Salivary samples were obtained immediately after awakening (08:00) and every 3 h until 20:00 on Day 1 in order to establish Baseline cortisol rhythms after a full night's sleep (5 samples). A sixth salivary sample was taken 30 min after awakening (08:30) in order to measure the peak level of cortisol associated with the CAR that is

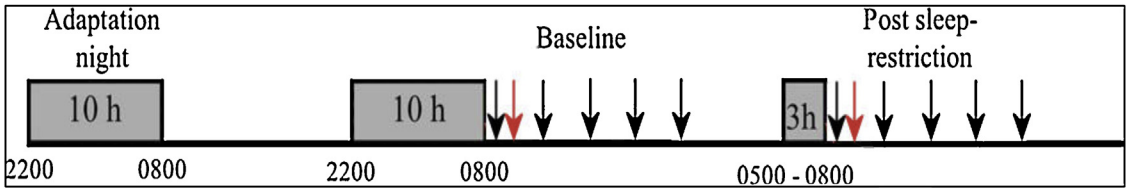

Figure 1 Filled rectangles represent the sleep opportunities for participants. Salivary samples for cortisol, and self-reports related to Hunger and Mood were obtained at the times indicated by arrows. Black arrows indicate saliva samples and Mood and Hunger questionnaires at 3 h intervals from 08:00 to 22:00. Red arrows indicated the 08:30 saliva samples used to assess the CAR. (For interpretation of the references to color in this legend, the reader is referred to the web version of the article.)
Source: Adapted from Omisade et al. (2010).

normally observed at approximately that time (Pruessner et al., 1997). Other saliva samples were taken for additional hormone assays, but these results have not yet been analyzed and are not included in this report.

Saliva was collected in two 2.0 mL vials using the passive drool collection method. Participants were instructed to pool saliva in their mouths and use a straw to drool into each vial. After 5 min, saliva samples were collected, frozen immediately at −20 °C and stored in the laboratory for two days, then transported frozen to another laboratory, where they were stored at −20 °C for up to 6 months before being thawed and assayed.

On the third night (Night 3), participants were kept awake during the first part of the night in the company of a research assistant and were allowed to sleep in the same bedroom only from 05:00 to 08:00. This restriction paradigm was chosen for several reasons: 1. Allowing some sleep provided a wake-up event to ensure that there was a CAR; 2. Wake timing was kept identical on both experimental days; 3. Restriction was severe enough to affect cortisol rhythmicity in women (as previously shown; Omisade et al., 2010); and 4. This level of sleep restriction might occur periodically in this age group, so it has relevance to peoples' spontaneous behavior.

During the period up to 05:00, participants watched movies, went for walks within the hospital or read books to stay awake. During this period, they were exposed to ordinary room lighting within the hospital (∼450 lux at eye level). They were not allowed to eat during the period of sleep restriction (22:00—05:00) and were only permitted to drink water. Salivary sampling on an identical schedule was repeated in the laboratory during the following day (Day 2; Post-sleep restriction).

During the early afternoon (∼13:00—14:00) of the Baseline and Post-sleep restriction days, participants in both groups went for a walk outdoors with an experimenter and were therefore exposed to ambient outdoor lighting. During these two days, participants were also asked to complete questionnaires each time they provided a saliva sample. They were asked to rate their levels of hunger on 10 cm scales, where 0 represented 'not at all' and 10 represented 'extremely' hungry. These scales were shown previously to be sensitive to effects of sleep loss on hunger in men (Spiegel et al., 2004a). The hunger scale is not a formal assessment instrument, so its psychometric properties have not been evaluated. Participants were also asked to rate their mood states using the Profile of Mood States (POMS) questionnaire. The POMS contains 65 items comprising 6 factors that reflect various mood domains (tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia, vigor-activity, and confusion-bewilderment). It was designed to measure general psychological distress in healthy, psychiatric, and physically ill populations (McNair et al., 1971). Fig. 1 illustrates the three-night and two-day protocol along with times of saliva sampling.

All participants were provided with regular meals that they selected from a predetermined menu. Menu items were selected from choices that were broadly consistent with participants' usual diets and with Canada Food Guide recommendations. They were not allowed any caffeine, sugary or 'junk food', or foods high in saturated fats. Food intake for both days was closely matched. Participants were provided with the same menu items in the same amounts on both days and required to finish each meal. The only differences in meals allowed between the two days were substitutions of types of fruit, vegetable or fruit juice, but the amounts and kinds of foods consumed were otherwise identical during the two laboratory days.

2.3. Data analysis

2.3.1. Hormone assays

Saliva samples from all 18 participants were thawed and used for cortisol and progesterone assays at the same time. The concentrations of cortisol in saliva samples collected at each time point and of progesterone (from an evening sample) were measured using commercially available enzyme-linked immunosorbent assays (ELISAs) for each hormone. All samples were analyzed in duplicate. The cortisol concentration in saliva was determined with a kit specifically designed to measure cortisol in saliva (High Sensitivity Salivary Cortisol ELISA, no. 1-3002; Salimetrics™, USA), based on the competitive binding ELISA technique. Cortisol standard curves were constructed in the range of 0.012—3.0 μg/dL, using standards supplied by the manufacturer. The inter-assay coefficient of variation (CV) was 1.9%. Procedures were performed in accordance with the salivary cortisol EIA kit insert no. 1-3002 supplied by the manufacturer.

Progesterone concentrations in saliva were determined using a similar commercially available ELISA from the same manufacturer (Salivary progesterone ELISA, no. 1-1502), based on the same competitive binding technique. Progesterone standards were constructed in the

range of 10—2430 pg/mL using standards supplied by the manufacturer. The inter-assay CV was 6.6%. Procedures were performed in accordance with the salivary progesterone EIA kit insert no. 1-1502 supplied by the manufacturer.

2.3.2. Statistical analyses

All statistical analyses were performed with the program SPSS for Windows, version 17. The threshold for statistical significance was set at $p = 0.05$, unless otherwise specified, and all tests were two-tailed. The following general approach to statistical analysis was taken. Normality of data distribution was assessed for each level of the analyzed variables. If the assumption of normality of distribution was violated, a non-parametric statistical model was used. Equality of error variances between the two groups (follicular and luteal) was also tested for each level of the analyzed variables prior to conducting between-group comparisons. When the latter assumption was violated, a test with 'equality of variances not assumed' was used.

The main outcome measures were the concentrations of cortisol measured on Day 1 (Baseline) and Day 2 (Post-sleep restriction). Baseline values from each of the six time points on Day 1 were compared between the two menstrual phase groups to determine whether women under normal sleep conditions show different cortisol patterns. To assess whether the CAR differed between groups at Baseline or in response to sleep restriction, the measure used was the area under the curve with respect to ground (AUCg); this refers to the amount of hormone calculated as values above zero (or above the lower limit of detection). The area measured was based on the samples collected at 08:00 and 08:30 (CAR-AUCg; Pruessner et al., 2003). To assess whether afternoon/evening cortisol levels differed between groups or after sleep restriction, an AUCg was calculated based on salivary cortisol values obtained between 14:00 and 20:00 (afternoon/evening-AUCg; Fig. 2; Pruessner et al., 2003). An alternative approach to measuring changes in hormone levels is to measure area under the curve with respect to increase (AUCi). This term refers to the amount of hormone (AUC) expressed as an increase over a defined initial value (e.g., increase from 08:00 to 08:30; CAR-AUCi).

Two 2×2 mixed ANOVAs were used to evaluate the effects of sleep loss and menstrual cycle phase on the CAR and afternoon/evening-AUC cortisol values. The between-subjects factor was group with two levels (follicular and luteal phase), and the within-subjects factor was sleep condition with two levels (Baseline day and Post-sleep restriction day). An effect size was calculated for all results that demonstrated statistical significance using Cohen's *d* calculation. Secondary analyses examined the effect of sleep condition and its interaction with menstrual cycle phase on the self-reported ratings of mood-state variables (POMS scores) and hunger ratings using 2×2 mixed ANOVAs. We also examined the correlations between cortisol values on Day 1 and progesterone values, as well as between cortisol values and self-reported hunger and mood scores. Similar correlations were examined using difference scores for cortisol and hunger and mood ratings between the Baseline and Post-sleep restriction days.

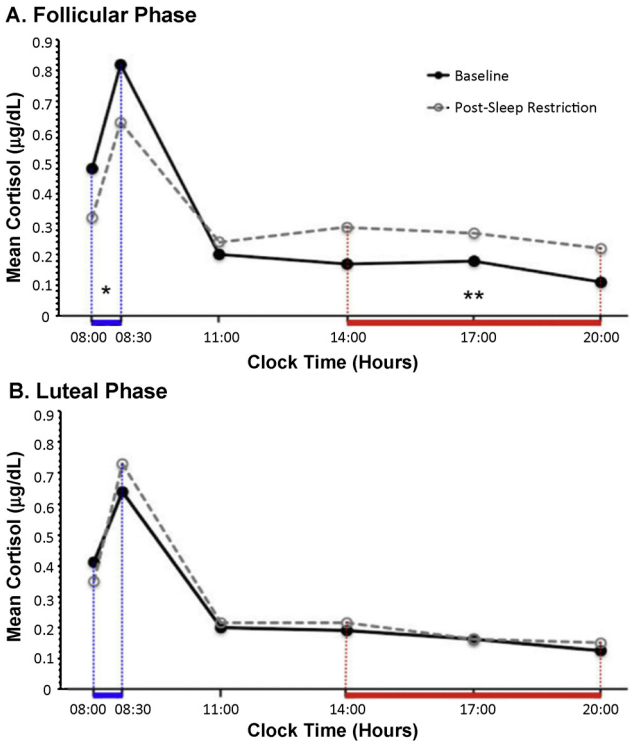

Figure 2 Mean salivary cortisol concentration across time of day for Baseline (●) and Post sleep-restriction (○) days for (A) follicular phase group ($n = 9$) and (B) luteal phase group ($n = 9$). The blue, vertical dotted lines and horizontal solid line indicate the times analyzed to measure the amplitude of the cortisol awakening response (CAR; 08:00—08:30). The red, dotted vertical lines and solid horizontal line indicate the times analyzed to assess the amplitude of the afternoon/evening area under the curve (AUCg; 14:00—20:00). Asterisks indicate statistically significant differences between the Baseline and Post sleep-restriction days for the CAR-AUCg and afternoon/evening-AUCg; *$p = 0.004$, by paired *t* tests; **$p = 0.008$, by Wilcoxon tests. (For interpretation of the references to color in this legend, the reader is referred to the web version of the article.)

3. Results

3.1. Sample characteristics

Habitual sleep patterns prior to the laboratory study were assessed using actigraphy (zero-crossing mode) and daily sleep diaries. Diaries were used in part to ensure that sleep/wake times, naps and times spent not wearing the actigraph (e.g., while showering) corresponded in the self-report and actigraphy data. There were no obvious discrepancies noted between the two measures for any participant. Habitual sleep patterns were characterized by averaging sleep parameters over 7 nights before the laboratory study, except for 4 individuals in the follicular group and 2 in the luteal group, for whom data were available for only 5—6 nights. Estimated sleep durations based on actigraphy for habitual sleep and for Baseline and sleep-restriction nights are shown in Table 1.

Women in the follicular group had an average BMI of 22.1 (range: 18—24.5) and those in the luteal group had an average BMI of 22.8 (range: 19.2—24.3), except for one with a BMI of 29.1; removing her data had no effect on any statistical outcome, so the data were retained in the analysis.

Participants' habitual food consumption patterns during the week before the study were assessed using their food diaries. Participants typically ate 3 meals a day and snacked between meals, although some participants skipped a few meals over the course of the week.

Menstrual cycle phase was established using three approaches: (1) Day 1 of participants' cycles was predicted based on self-reports of their preceding 2—5 cycles; this estimate was used to schedule the participants for their laboratory experiment. (2) After they had participated in the experiment, they reported the timing of Day 1 of their next cycle to the experimenter. (3) Progesterone levels were assayed using a saliva sample obtained during the first night of the laboratory phase of the study; group averages are presented in Table 1, and each participant's progesterone level is shown in Supplementary Table S1.

Two women in the luteal phase group had progesterone levels that fell outside the normative, expected range (>200 pg/mL) for their assigned phase (Supplementary Table S1). This range was provided by the assay manufacturer and has been confirmed by other studies (Gandara et al., 2007). For each of these participants, her phase assignment was consistent with the timing of prior menstrual cycles and her subsequent report of onset of menses after participation in the study. Removing their data had no effect on the statistical results or conclusions, so their data were retained in their assigned groups. Absolute levels of progesterone are not as consistent among women as is the relative rise in levels after ovulation. Since we did not have progesterone levels from both phases for each participant, we could not determine whether the levels obtained for these two women were atypical for them, but the evidence from their pre- and post-study cycles indicates that their phase assignments were appropriate.

One participant started her subsequent menstrual cycle 10.5 days earlier than anticipated based on her previous cycles, which would suggest that she was at a later stage of her assigned cycle than expected when she was studied. Her progesterone level was consistent with her assigned follicular menstrual phase and her cortisol data were characteristic of this group as well. Removing her values from the cortisol analyses did not change any statistical results or conclusions, so her data were retained in the analysis.

Means, standard deviations and sample sizes for both groups are presented in Table 1 for the following variables: age at the time of study, BMI, progesterone values, average habitual sleep duration before the study, and average sleep duration during the two experimental nights, as assessed by actigraphy.

3.2. Comparisons of Baseline cortisol between menstrual phases

Means and standard deviations for hormone measures on each day for AUCg were calculated for both the CAR and afternoon/evening cortisol values, and AUCi values were calculated for the CAR (Table 2). In addition, the mean changes in AUCg and AUCi for the CAR between the two days were calculated by subtracting equivalent values on the Post-sleep restriction day from values on the Baseline day for each individual (Table 2).

Cortisol values and the results of the statistical analyses are presented in Table 2. There were no significant differences between the two menstrual phase groups in cortisol values at any of the six times assayed on the Baseline day. There were significant main effects of sleep condition for both CAR-AUCg and afternoon/evening-AUCg cortisol values. On the Post-sleep restriction day, there was a significant decrease ($p = 0.01$) in mean cortisol CAR-AUCg and a significant increase ($p = 0.001$) in mean cortisol afternoon/evening-AUCg cortisol. There was also a Group × Day interaction for both dependent variables: CAR-AUCg ($p = 0.005$) and afternoon/evening-AUCg cortisol ($p = 0.006$) values.

To follow up the Group × Day interaction and the main effect of Sleep Condition for the CAR-AUCg and afternoon/evening-AUCg cortisol, paired-sample *t*-tests were performed for the follicular and luteal groups, comparing their Baseline and Post-sleep restriction values for CAR-AUCg. Afternoon/evening cortisol AUCg values after sleep restriction were not normally distributed, so the Baseline and Post-sleep restriction values for afternoon/evening AUCg were compared in each group using the non-parametric Wilcoxon signed-rank test. Comparisons within the luteal group revealed no significant change in either CAR-AUCg or afternoon/evening-AUCg cortisol values ($p > 0.05$). In the follicular group, there was a significant decrease from Baseline to Post-sleep restriction in CAR-AUCg ($p = 0.004$; $d = 1.019$) and a significant increase in afternoon/evening-AUCg ($p = 0.008$; $d = 1.473$) (Fig. 2; Table 2).

Using the measure of CAR-AUCi, there was no significant effect of Sleep Condition for either menstrual phase group ($p > 0.05$). As illustrated in Fig. 2B, the peak cortisol value at 08:30 on the Post-sleep restriction day was reduced relative to the Baseline day for the follicular but not the luteal group. However, this peak rose from a lower starting value at 08:00 after sleep restriction in the follicular group, so the increases were parallel on the two days, resulting in no change in AUCi.

3.3. Hunger and mood scores

Self-rated Hunger and Mood scores were compared between the two days using a 2 × 2 mixed ANOVA for all participants ($n = 18$), which revealed a significant increase in Hunger on the Post-sleep restriction day (see Table 3), but no significant main effect of Group or Group by Sleep Condition interaction. To assess whether this effect was consistent across time of day, hunger ratings were grouped into morning values (08:00 and 11:00), afternoon values (14:00) and evening values (17:00 and 20:00). Ratings during these three periods were compared between days using Bonferroni-adjusted alpha levels of 0.017 per test (0.05/3). Results indicated that there was a significant effect of sleep restriction on evening

Table 2 Salivary cortisol levels and area under the curve calculations.

Measure	Day	Phase	Mean (SD)	*F*	*p*
Cortisol					
08:00	Baseline	Follicular	0.48 (0.19)	0.181	0.398
		Luteal	0.41 (0.14)		
08:30	Baseline	Follicular	0.82 (0.21)	2.906	0.108
		Luteal	0.64 (0.23)		
11:00	Baseline	Follicular	0.20 (0.07)	0.070	0.795
		Luteal	0.20 (0.05)		
14:00	Baseline	Follicular	0.17 (0.08)	0.301	0.591
		Luteal	0.19 (0.07)		
17:00	Baseline	Follicular	0.17 (0.06)	0.786	0.388
		Luteal	0.16 (0.07)		
20:00	Baseline	Follicular	0.11 (0.05)	0.787	0.388
		Luteal	0.12 (0.03)		
CAR (AUCg)	Baseline	Follicular	0.32 (0.08)		
		Luteal	0.26 (0.08)		
	Post-sleep restriction	Follicular	0.24 (0.09)		
		Luteal	0.27 (0.10)		
Sleep condition				**8.394**	**0.011***
Group × sleep condition				**10.825**	**0.005***
CAR (AUCi)	Baseline	Follicular	0.08 (0.06)		
		Luteal	0.06 (0.06)		
	Post-sleep restriction	Follicular	0.08 (0.06)		
		Luteal	0.10 (0.06)		
Sleep condition				2.139	0.163
Group × sleep condition				10.825	0.094
Afternoon—Evening (AUCg)	Baseline	Follicular	0.93 (0.26)		
		Luteal	0.96 (0.29)		
	Post-sleep restriction	Follicular	1.57 (0.55)		
		Luteal	1.02 (0.21)		
Sleep condition				**15.315**	**0.001***
Group × sleep condition				**10.241**	**0.005***

Cortisol measures at each time point (μg/dL) on the Baseline day and results of one-way ANOVAS comparing women in the follicular and luteal groups. Values for the cortisol awakening response (CAR) and Afternoon—Evening levels are given as μg of cortisol calculated as area under the curve with respect to ground (AUCg) or with respect to increase (AUCi) on the baseline and post-sleep restriction days, as a function of menstrual cycle phase. Results are shown from a 2 × 2 Mixed ANOVA for cortisol CAR and afternoon/evening-AUCg and AUCi, showing the main effect of the sleep condition (Baseline and Post-sleep restriction days), and the interaction between sleep condition and menstrual phase group. Values that differed significantly on the Post-sleep restriction day compared to Baseline are shown in bold and marked by an asterisk.

hunger scores ($p = 0.012$; $d = 0.718$), but not on morning or afternoon hunger scores (Fig. 3).

The effects of sleep restriction on seven mood variables in the POMS (anger, depression, vigor, fatigue, confusion, tension and total mood disturbance) were assessed using Bonferroni-adjusted alpha levels of 0.008 per test (0.05/6). Seven 2 × 2 mixed ANOVAs were performed in order to evaluate the effects of sleep restriction on the mood variables. The ANOVAs revealed that sleep restriction increased fatigue scores and decreased vigor scores. In addition, total mood disturbance (calculated by adding scores for all negative mood states and the inverse scores of all positive mood states) also increased significantly. There was no main effect of Group and no significant interaction between Group and sleep condition, indicating that sleep restriction had similar effects on mood scores in both groups (Table 3).

3.4. Correlations among endocrine and behavioral variables

Bivariate correlations were computed between each cortisol value measured on the Baseline day and the mood and hunger ratings obtained at the same time of day. In addition, the change in cortisol at each time point (Day 1—Day 2 value) was similarly correlated with the changes in mood and hunger ratings at corresponding time points. There were no significant correlations of either Baseline cortisol values or difference scores with hunger and mood ratings. There were also no significant correlations between individuals' progesterone levels and their Baseline CAR-AUCg and afternoon/evening-AUCg values, or the differences between these measures on the two days. Finally, bivariate correlations were computed for Baseline and

Table 3 Participant ratings of hunger, fatigue and vigor.

Measure	Day	Phase	Mean (SD)	*F*	*p*
Hunger	Baseline	Follicular	3.91 (1.33)		
		Luteal	3.83 (0.89)		
	Post-sleep restriction	Follicular	5.01 (1.14)		
		Luteal	4.53 (0.83)		
Sleep condition				**22.769**	**<0.001***
Group × Sleep condition				1.124	0.306
Fatigue	Baseline	Follicular	4.16 (2.15)		
		Luteal	4.75 (3.90)		
	Post-sleep restriction	Follicular	6.35 (3.81)		
		Luteal	6.14 (6.07)		
Sleep condition				**12.06**	**0.004***
Group × Sleep condition				0.163	0.782
Vigor	Baseline	Follicular	12.9 (5.01)		
		Luteal	14.5 (5.93)		
	Post-sleep restriction	Follicular	9.11 (4.20)		
		Luteal	8.33 (4.30)		
Sleep condition				**13.73**	**0.002***
Group × sleep condition				0.063	0.806

Ratings of hunger, fatigue and vigor averaged over 5 time points across each Baseline and Post-sleep restriction day for women in the follicular ($n = 9$) and luteal ($n = 9$) phase groups. Results are shown from the 2 × 2 Mixed ANOVA for hunger and 2 × 2 Mixed ANOVA for fatigue and vigor. Values that differed significantly on the Post-sleep restriction day compared to Baseline are shown in bold and marked by an asterisk.

difference scores for hunger ratings (averaged over the day) with each of the seven POMS mood variables (also averaged). The only statistically significant correlation was a robust positive correlation between the change in self-reported hunger between days and the change in self-reported fatigue ($r_{16} = 0.68$, $p = 0.007$).

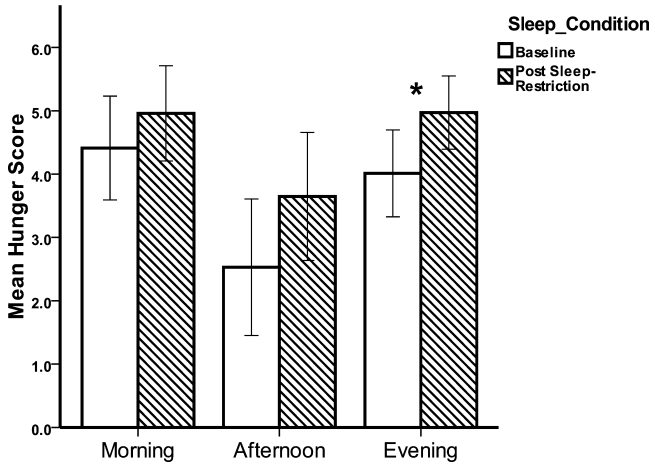

Figure 3 Mean (±95% CI) scores for self-rated hunger at different times of day at Baseline (after a 10 h sleep opportunity) and Post sleep-restriction (after a 3 h sleep opportunity) for all participants ($n = 18$). Morning: 08:00—11:00, Afternoon: 14:00, and Evening: 17:00—20:00. Hunger on the two days was compared using a paired *t* test for each time period; *$p = 0.001$.

4. Discussion

4.1. Impact of menstrual cycle phase on cortisol responses to sleep loss

The primary objective of this study was to assess whether menstrual cycle phase modulated the effects of sleep loss on the daily rhythm of cortisol secretion. Women during their follicular phase showed a significant reduction in the morning CAR-AUCg after sleep restriction, whereas those in the luteal phase did not. As shown in Fig. 2B, this reduction in cortisol during the CAR resulted from a lower initial level at waking, rather than from a slower rise between waking (08:00) and the 08:30 sample. The parallel rise before and after sleep restriction, and the confirmation that the CAR-AUCi did not change significantly, indicate that sleep loss did not affect the mechanism of the CAR, but rather the initial level at waking.

It is likely that sleep restriction during the follicular phase, but not the luteal phase, altered the rate at which cortisol rose from its nadir during the second half of the night. One limitation of this study, inherent in the use of salivary sampling, is that cortisol was not measured from 20:00 to 08:00. Measuring blood levels during this period would clarify how nocturnal cortisol secretion in women is affected by sleep loss at different menstrual cycle phases.

Although morning cortisol levels have not been a focus of most previous studies on the effects of sleep deprivation, published data from men indicate that they may also show attenuated peak cortisol levels after sleep loss. After one or six nights of partial sleep deprivation, morning peak cortisol

levels may also have been reduced in men (Fig. 1 in Leproult et al., 1997; Fig. 1B in Spiegel et al., 2004b), but the fact that waking occurred at different clock times in different sleep conditions makes direct comparisons difficult. Similarly, overnight complete sleep deprivation in 6 men resulted in a trend toward a lower average cortisol level at 07:00 that was not statistically significant (Kavčič et al., 2011; personal communication, P. Kavčič, April, 2014). Lower morning cortisol levels have been correlated with increased body weight in men (Praveen et al., 2011); sleep loss decreased morning cortisol levels in women in the follicular phase in this study, which may contribute to an increased risk for weight gain, obesity, and other metabolic disorders.

Elevation of cortisol levels during the afternoon and evening after partial or total sleep loss has been reported consistently in numerous previous studies involving both men (e.g., Spiegel et al., 2004a; Leproult et al., 1997) and women (Omisade et al., 2010). This is the first study that examined whether the increase in cortisol at this time of day after sleep loss is affected by menstrual cycle phase. We found that the increase occurred robustly in women during the mid-follicular phase but was absent in those studied during the mid-luteal phase.

Elevated afternoon cortisol levels have been associated with alterations in glucose metabolism and insulin resistance that could promote weight gain, visceral obesity and other features of the metabolic syndrome (Plat et al., 1999; Whitworth et al., 2005; Anagnostis et al., 2009; Buxton et al., 2010; Matthews et al., 2012). Thus, the failure of women during the follicular phase to show the usual steep fall in cortisol levels during the afternoon after sleep restriction could contribute to findings of higher body weights in those with short sleep in several prospective epidemiological studies (Hasler et al., 2004; Patel et al., 2006).

One interpretation of the pattern of cortisol levels shown across the day after sleep restriction during the follicular phase is that the daily rhythm of cortisol secretion is dampened by sleep loss, reducing the morning peak and attenuating the afternoon fall in levels. Both the CAR and the steep fall in cortisol levels during the afternoon are presumably adaptive features of the regulation of cortisol. The CAR may mobilize metabolic resources demanded by the increase in activity and alertness required in the morning. The afternoon fall would prevent sustained high levels, such as those associated with chronic stress, from exerting deleterious effects on metabolism, as well as on the brain (Kyrou et al., 2006; Walker, 2006; Sapolsky et al., 1986; Stokes, 1995; Sheline et al., 2002), and would help prepare the individual for sleep. Sleep loss appears to impair both of these features of the normal daily cortisol rhythm during the follicular phase.

A key question is why the reduced amplitude of daily cortisol secretion observed in response to sleep loss in men (in previous studies) and in women during the follicular phase was absent in women during the mid-luteal phase. Differences in reproductive hormone levels in the follicular and luteal phases are the most obvious potential cause. Only progesterone levels were measured in this study, primarily to confirm the self-reported menstrual phases of the participants. We did not, however, observe any significant correlations between measured progesterone levels and changes in cortisol levels in either the morning or afternoon/evening in response to sleep loss. Other studies have reported no spontaneous differences in the cortisol daily rhythm between the follicular and late luteal phase, but noted changes in prolactin, luteinizing hormone and growth hormone that may be attributable to different progesterone levels (Caufriez et al., 2009). These findings suggest that these other hormonal changes might contribute to differences in cortisol responsiveness to sleep loss.

The lack of correlation between progesterone levels and changes in cortisol has to be interpreted cautiously because progesterone was only measured at one time of day, and there may be daily rhythms in levels, at least in the luteal phase (Caufriez et al., 2009). In addition, there are large individual differences in progesterone levels (Fujimoto et al., 1990), and the absolute values used in these correlations may be less relevant than the changes in levels across menstrual phases in individual women. This possibility could be addressed by measuring responses to sleep loss and changes in progesterone levels in individual women during both their follicular and luteal phases. While such correlational data would be informative, a more definitive study would evaluate how experimental manipulations of progesterone and/or estrogen levels affect endocrine responses to sleep restriction. A role for reproductive hormones was also hinted at in unpublished data from Omisade et al. (2010), in which the cortisol patterns of women taking oral contraceptives showed responses to sleep loss that were intermediate between those of women presumed to be in the follicular and luteal phases of spontaneous menstrual cycles.

Another issue with respect to the differences in responses to sleep loss during different menstrual cycle phases is that the average peak value of cortisol at 08:30 (and thus the CAR) on the Baseline day appeared to be lower in the luteal phase than in the follicular phase (Fig. 2), although this difference was not statistically significant. The number of participants studied and variability at a time of day when cortisol levels are changing rapidly may have contributed to the lack of statistical significance. Morning cortisol levels during the luteal phase might be shown to be significantly lower than during the follicular phase in a larger study. It is not clear, however, how this would contribute to the failure to see a further attenuation of morning levels after sleep loss. The smaller peak morning levels during the luteal phase in this study are still much higher than afternoon levels, so a further reduction in level, and therefore a smaller CAR, would seem physiologically possible starting from this lower Baseline.

The absence of an afternoon increase in cortisol levels after sleep loss in the luteal phase clearly cannot be attributed to Baseline differences at that time of day, since Baseline values were very similar in both groups. Increased progesterone levels or other endocrine changes (Caufriez et al., 2009) during the luteal phase may buffer the responses of the hypothalamic—pituitary—adrenal (HPA) axis to sleep loss in the afternoon.

4.2. Impact of menstrual cycle phase and sleep loss on hunger and mood

There were no menstrual phase differences in hunger ratings or mood during the Baseline day. Most reports of

menstrual-cycle related appetite changes relate to appetite changes during the premenstrual (~5 days before menses onset) or menstrual phase (Barr et al., 1995; Li et al., 1999; Pelkman et al., 2000; Davidsen et al., 2007), which were not evaluated in the present study.

Similar to previous studies that involved one or two nights of sleep restriction (Spiegel et al., 2004a; Brondel et al., 2010), we found a statistically significant increase in hunger during the evening hours for all participants; there were no differences related to menstrual phase. Although not all results have been consistent, most studies have reported that sleep loss increased levels of the hunger-promoting hormone ghrelin, increased appetite when food access was limited, and increased food intake when it was freely available (Spiegel et al., 1999, 2004a, 2005; Schmid et al., 2008; Bosy-Westphal et al., 2008; Pejovic et al., 2010; Markwald et al., 2013).

One interpretation that accounts for both previous results and the present findings is that increases in hunger after sleep loss are a physiological and behavioral adaptation to obtain additional calories needed to sustain activities during extended hours of waking (when most of the intake occurs; Markwald et al., 2013). This view is strengthened by the observation that hunger was significantly elevated only during the evening, when participants would have been most affected by the length of prior waking. In addition to this homeostatic mechanism, it is also possible that sleep loss affects less clearly defined non-homeostatic mechanisms, such as those related to the impact of mood (seeking 'comfort food') and reduced inhibition that may be associated with increased fatigue.

A single night of sleep restriction was associated with statistically significant decreases in self-reports of the positive mood state vigor, increases in self-reports of the negative mood state fatigue, and increases in the measure that assesses overall mood state (total mood disturbance). These differences were not affected by menstrual cycle phase. The observed changes were related to perceived energy level rather than to other aspects of mood regulation, such as sadness or anger, and ratings fell within the normal range for the general population. There were no changes in measures of tension-anxiety or any other scales that might reflect an increase in self-perceived stress level, similarly to what has been reported previously in men (Spiegel et al., 2004b).

There was a robust positive correlation between changes in self-reported fatigue and in self-reported hunger after sleep loss. One interpretation of these findings is that increased fatigue leads to a perceived need for more energy, which is expressed as increased hunger. Previous research demonstrated a link between partial sleep restriction and hunger by showing that sleep loss was associated with increases in both energy expenditure and energy intake, but that intake over-compensated for the increased expenditure, leading to weight gain that was detectable over as little as a five-day period of sleep restriction (Markwald et al., 2013).

4.3. Effects of light exposure

While awake at night during sleep restriction, participants were exposed to typical artificial light levels in the laboratory (~450 lux) until 05:00; this value probably represents a maximum exposure level, since they moved about and engaged in various activities that did not involve deliberate light exposure. This situation would be characteristic of individuals who are awake voluntarily during the night, but it raises the question of what effect this additional light exposure might have had on cortisol levels.

Nocturnal light exposure is known to affect the human circadian system, and intensities in the range of 100—500 lux have been reported to produce modest to large declines in melatonin levels as well as phase delays in the melatonin rhythm in both men and women (Nathan et al., 1997; Zeitzer et al., 2000). Nocturnal bright light exposure (~10,000 lux) has also been reported to decrease cortisol levels, while intensities less than 5000 lux appear to have little or no effect (see Jung et al., 2010 for a review). The suppressive effect of 10,000 lux light on cortisol was reversed within less than 1 h after termination of the bright light exposure (Jung et al., 2010).

These findings suggest that ordinary room light exposure in this study would have been unlikely to affect cortisol levels during the night; nor would any possible effect have been sustained through the subsequent 3 h of sleep in darkness. In addition, a study in which men were exposed to light of 50 lux intensity during a night of continuous sleep deprivation also showed a tendency toward blunting of the morning cortisol peak and elevated levels in the afternoon (Kavčič et al., 2011; Fig. 2, although these changes were not statistically significant in this small sample). These results reinforce the conclusion that the similar changes in cortisol we observed were not related to the brightness of the nocturnal illumination.

The changes in cortisol levels after sleep loss and light exposure in follicular phase participants are also not consistent with a light-induced, acute phase delay of the circadian cortisol rhythm. Any such delay would have been quite small at this light intensity and would have been counteracted by morning light exposure. At most this might have resulted in a small delay in reaching the afternoon trough, achieved during the Baseline day by 14:00. Instead cortisol levels after sleep loss were still elevated above this level as late as 20:00, the last sample taken.

Participants were also exposed to ambient outdoor lighting during a short (maximum of 1 h) early-afternoon walk. In a previous study, afternoon light exposure (4500 lux at eye level for 3 h) had no significant effect on afternoon cortisol levels (Leproult et al., 2000). Outdoor light intensities were not monitored in the present study, but these would likely have been moderate during January—April in Halifax. Since similar light exposure occurred on both days of the study, it is not likely to have contributed to cortisol elevation in the afternoon in women during the follicular phase after sleep loss. In addition, participants in both menstrual cycle phases were exposed to the same lighting conditions during both the night and the afternoon, so these are unlikely to have contributed to the menstrual phase difference in responsiveness to sleep restriction.

4.4. Summary, limitations and conclusions

Restriction to a 3 h sleep opportunity for a single night altered the daily rhythm of salivary cortisol during the

next day, reducing the amplitude of the morning CAR and increasing afternoon—evening levels in women during the mid-follicular phase of their menstrual cycles. Neither effect was observed among women in the mid-luteal phase. Although there were no significant group differences in cortisol levels across time of day before sleep restriction, there appeared to be a lower morning level of cortisol during the mid-luteal phase at Baseline that may not have reached significance because of the small number of women studied. Further characterization of menstrual phase differences in the response of the cortisol circadian rhythm to sleep loss would benefit from sampling plasma cortisol levels throughout 24 h periods.

Levels of progesterone differed between the two groups studied, but there was no significant correlation between progesterone levels assessed at one time of day and the changes in cortisol levels induced by sleep restriction. It may be that there is no direct relationship between progesterone levels and cortisol patterns, or that variations in progesterone levels within a day, or among women, obscured such correlations.

Another limitation is that we characterized responses to sleep loss at only two time points within the spontaneous menstrual cycles of young women. Fully characterizing the impact of the menstrual cycle on the consequences of sleep loss will require studies across other phases of the cycle, and in women in other reproductive conditions, including while taking hormone-based contraceptives, during pregnancy, and in the post-menopausal period. In addition, each woman was studied at only one menstrual cycle phase. Given differences in hormone levels among women, use of a within-participant design with individuals tested at both phases would strengthen interpretation of the results. In addition, balancing the order of treatments (10 h and 3 h sleep opportunities), with sufficient recovery time after sleep restriction, could strengthen the study design.

There were no differences observed in hunger or mood between the two groups studied. It remains to be assessed whether the effects of sleep loss on these measures are modified during other phases of the menstrual cycle, in particular during the premenstrual and menstrual phases, when some spontaneous appetite differences have been reported.

The results of this study support the need to integrate research on women and their physiology, including aspects that differ significantly from the physiology of men, into sleep- and metabolism-related research. The relative exclusion of women, especially those in their reproductive years, from health-related research has been noted previously (Correa-de-Araujo, 2006), as well as a similar exclusion of other female mammals from biological research (Beery and Zucker, 2011). Further research into the physiological changes in women following sleep loss may ultimately provide a better understanding of how reductions in hours of sleep affect risks for weight gain and hormonal disruption, as well as the development of associated chronic diseases in women, and may ultimately improve diagnosis and treatment of women's health problems.

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Conflict of interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2014.06.002.

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